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ORIGINAL ARTICLE

Prenatal Genetic Diagnosis of Williams-Beuren Syndrome with Atypical and Complex Phenotypes

Weiqiang Liu [1, 3, *], Haibing Zhong [1, 5, *], Dingya Cao [2, *], Jinshuang Song [4], Tong Zhang [1, 3], Shuxian Zeng [1, 3], Xiaoyi Cong [1, 3], Min Chen [2]

[*] *These authors contributed equally to this work*
[1] *Central Laboratory, Longgang District Maternity & Child Healthcare Hospital of Shenzhen City (Longgang Maternity and Child Institute of Shantou University Medical College), Shenzhen, China*
[2] *Department of Fetal Medicine and Prenatal Diagnosis, Key Laboratory for Major Obstetric Diseases of Guangdong Province, Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, China*
[3] *Shenzhen Longgang District Key Laboratory for Birth Defects Prevention, Shenzhen, China*
[4] *Department of Medical Ultrasonics, Longgang District Maternity & Child Healthcare Hospital of Shenzhen City (Longgang Maternity and Child Institute of Shantou University Medical College), Shenzhen, China*
[5] *Department of Laboratory Medicine, Longgang Central Hospital of Shenzhen, Shenzhen, China*

SUMMARY

Background: **Williams-Beuren syndrome (WBS) is a severe congenital disorder that presents challenges in prenatal diagnosis due to the atypical or incomplete phenotypes exhibited by affected fetuses. This study investigated the relationship between genotype and complex phenotype in WBS fetuses using ultrasound, SNP array, and whole exome sequencing.**

Methods: **Chromosomal microarray analysis (CMA) and whole genome sequencing (WES) were conducted on pregnant women undergoing prenatal diagnosis. We analyzed genome-wide copy number variants (CNVs), regions of homozygosity (ROH), single nucleotide variants (SNVs), small insertions and deletions, and splice sites.**

Results: **A deletion at 7q11.23 was identified in 7 out of 6,718 prenatal diagnostic samples (1 in 960). Ultrasound findings varied: two fetuses exhibited cardiovascular anomalies; one presented with persistent left superior vena cava and intrauterine growth retardation (IUGR), while two others displayed polycystic kidney dysplasia, one accompanied by mild tricuspid regurgitation, and the remaining two fetuses showed no apparent ultrasound abnormalities. Genetic analysis revealed CNVs ranging in size from 1.43 to 1.66 megabase pairs (Mb), affecting 34 to 41 genes. On average, one additional CNV larger than 100 kilobase pairs (Kb) of unknown significance and 0.43 ROH larger than 5 Mb were identified in these cases. Although pathogenic or likely pathogenic SNV or splice sites related to renal development and cardiovascular development were found, none correlated with the fetal phenotype observed.**

Conclusions: **The phenotypes of WBS fetuses are often atypical and complex. Future research should focus on integrating advanced genetic technologies and improved imaging modalities to enhance our understanding of the intricate genotype-phenotype relationships associated with WBS.**

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Correspondence:
Weiqiang Liu
Central Laboratory
Longgang District Maternity & Child Healthcare Hospital of Shenzhen City
(Longgang Maternity and Child Institute of Shantou University Medical College)
6 Ailong Road, Shenzhen City
China
Phone: + 86 075528933003
Email: liuwq06@126.com

Min Chen
Department of Fetal Medicine and Prenatal Diagnosis
Key Laboratory for Major Obstetric Diseases of Guangdong Province
Third Affiliated Hospital of Guangzhou Medical University
63 Duobao Road, Guangzhou City
China
Phone: + 86 2081292292
Email: edchen99@gmail.com

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Supplementary Data

Table S1. WES results of fetal samples from 4 cases of WBS.

Case	Chromosome position	Gene	Nucleotide changes	Amino acid changes	Zygosity	Interpretation	Related disease/phenotype
Case 1	3:9979763	*CRELD1*	c.433G>A (NM_015513)	p.A145T	Het.	VUS	Atrioventricular septal defect, partial, with heterotaxy syndrome, (MIM:606217, AD)
	8:65517310	*CYP7B1*	c.1162C>T (NM_001324112)	p.R388 *	Het.	P	Bile acid synthesis defect, congenital, 3 (MIM:613812AR) Spastic paraplegia 5A (MIM:270800, AR)
	9:6553457	*GLDC*	c.2368C>T (NM_000170)	p.R790W	Het.	LP	Glycine encephalopathy 1 (MIM:605899, AR)
Case 2	17:29253883	*ADAP2*	c.282G>T	p.K94N	Hom.	VUS	/
	4:170482659	*NEK1*	c.1238T>C (NM_001199400)	p.L413P	Het.	VUS	Amyotrophic lateral sclerosis, susceptibility to, 24, (MIM:617892, AD)
	6:51923353	*PKHD1*	c.1280C>T (NM_138694)	p.S427F	Het.	VUS	Polycystic kidney disease 4, with or without hepatic disease (MIM:263200, AR)
	10:115373936	*NRAP*	c.3300+6T>C (NM_001322945)	/	Het.	VUS	Biallelic loss-of-function mutations in NRAP could constitute a low-penetrance genetic risk factor for cardiomyopathy (OIMI:602873, AR)
	10:115381896	*NRAP*	c.2393T>C (NM_001322945)	p.I798T	Het.	VUS	
	11:73872485	*C2CD3*	c.441dupT (NM_001286577)	p.T148Yfs*8	Het.	LP	Orofaciodigital syndrome XIV (mMIM:615948, AR)
	13:20763612	*GJB2*	c.109G>A (NM_004004)	p.V37I	Het.	P	Deafness, autosomal dominant 3A(MIM:601544,AD) Deafness, autosomal dominant 1A (MIM:220290,AR)
	18:32457718	*DTNA*	c.928G>T (NM_001198943)	p.A310S	Het.	VUS	Left ventricular noncompaction 1, with or without congenital heart defects (MIM:604169, AD)
Case 3	1:74808579	*FPGT-TNNI3K*	c.1078G>C (NM_001112808)	p.G360R	Het.	LP	Cardiac conduction disease with or without dilated cardiomyopathy (MIM:616117, AD)
	2:220283470	*DES*	c.286G>T (NM_001927)	p.A96S	Het.	VUS	Cardiomyopathy, dilated, 1I (MIM:604765, AD)
	5:39341378	*C9*	c.346C>T (NM_001737)	p.R116 *	Het.	P	C9 deficiency (MIM:613825) Macular degeneration, age-related, 15, susceptibility to (MIM:615591, AD)

Table S1. WES results of fetal samples from 4 cases of WBS (continued).

Case	Chromosome position	Gene	Nucleotide changes	Amino acid changes	Zygosity	Interpretation	Related disease/phenotype
Case 4	5:228417	*SDHA*	c.595A>G (NM_001294332)	p.I199V	Het.	VUS	Cardiomyopathy, dilated, 1GG (MIM:613642, AR) Pheochromocytoma/paraganglioma syndrome 5 (MIM:614165, AD)
	12:48258833	*VDR*	c.274G>A (NM_000376)	p.E92K	Het.	LP	Rickets, vitamin D-resistant, type IIA (MIM:277440, AR)
	11:71148969	*DHCR7*	c.852C>A (NM_001163817)	p.F284L	Het.	LP	Smith-Lemli-Opitz syndrome (MIM:270400, AR)
	12:121176944	*ACADS*	c.1031A>G (NM_000017)	p.E344G	Het.	P	Acyl-CoA dehydrogenase, short-chain, deficiency of (MIM:201470, AR)